1 ABSTRACT

Title

A prospective non-interventional post-authorisation safety study (PASS), designed as a disease registry of patients with transfusion dependent IPSS low or intermediate-1-risk myelodysplastic syndromes (MDS) and isolated del(5q)

Keywords

Lenalidomide, myelodysplastic syndromes, acute myeloid leukaemia, transfusion dependent, deletion 5q

Rationale and Background

Revlimid® (lenalidomide) is a drug belonging to the class of IMiDs® (a proprietary series of drugs with immunomodulatory and other properties) currently registered in more than 20 countries worldwide, including the European Union (EU), for the treatment of myelodysplastic syndromes (MDS) in adult patients who had received a previous therapy. Revlimid® received marketing authorisation in the EU with a condition for the marketing authorisation holder (MAH) to implement a non-interventional MDS post-authorisation safety study (PASS) into which patients who were prescribed commercial lenalidomide for MDS were enrolled to further characterise the risk of progression to acute myeloid leukaemia (AML) in patients treated with lenalidomide. This MDS PASS aimed to gather additional safety information in patients exposed and nonexposed to lenalidomide, especially regarding the risk of progression to AML, second primary malignancies (SPMs), and survival in a routine-care setting.

Research Question and Objectives

The primary research question addressed by this MDS registry (PASS) was whether the 2-year cumulative incidence of AML progression and mortality among transfusion-dependent International Prognostic Scoring System (IPSS) low- or intermediate-1 (int-1)-risk MDS patients with an isolated deletion 5q (del[5q]) cytogenetic abnormality treated with lenalidomide (labelled indication) in a routine-care setting after EU MDS indication authorisation differed from the incidence observed in Studies MDS-003 and MDS-004 combined. It also assessed whether the overall safety profile of lenalidomide differed between the clinical trials and routine-care patient populations.

Primary objective

- To ascertain the progression to AML and survival (through calculation of product-limit estimators and incidence rates, as well as the attributable risk [AR] and AR percentage [AR%]) among 217 patients (Primary population) with red blood cell (RBC) transfusion-dependent, IPSS low- or int-1-risk MDS with del(5q) as an isolated cytogenetic abnormality who had been treated with lenalidomide

Secondary objectives

- To describe the progression to AML and survival among patients with MDS who had never been exposed to lenalidomide. This included explorative analyses of progression to AML and

survival in patients receiving treatments or treatment modalities other than lenalidomide, whenever possible.

- To further characterise the safety profile of lenalidomide among MDS patients treated with lenalidomide through calculation of incidence measures for haematologic and non-haematologic adverse events (AEs), including infections, bleeding, thromboembolic events, major cardiac events, and SPMs other than AML (considered disease progression)
- To employ Cox proportional hazards models to evaluate risk factors associated with progression to AML and overall survival (OS) among MDS patients included in the Primary population who had been treated with lenalidomide
- To characterise the effectiveness profile of lenalidomide among MDS patients in the Primary population who were treated in a routine-care setting, especially erythroid response, transfusion independence, cytogenetic response, and related long-term outcomes (OS; incidence of non-leukaemic death; incidence of infections, bleeding, and cardiovascular events; and progression to AML)

Study Design

This PASS was designed as a non-interventional, disease registry (henceforth referred to in this report as "MDS registry [PASS]"). No deviation from the routine clinical practice of enrolled patients should have occurred as a result of this registry (PASS). Patients with transfusion-dependent IPSS low or int-1-risk MDS and isolated del(5q) who met the selection criteria were eligible for enrollment if they were diagnosed on 15-Jun-2007 (date of first approval of Revlimid in Europe) or later. All patients were followed up for 3 years after the informed consent date or until death or withdrawal of consent.

This study was an observational study not designed or powered to perform statistical comparison between patients exposed and not exposed to lenalidomide.

Setting

This study was conducted in 162 sites in the following countries: Spain, Italy, France, Germany, Belgium, Greece, Denmark, Sweden, Norway, Luxembourg, and the United Kingdom (UK).

All study visits were performed according to the standard clinical practice. Eligible patients were entered into the study and data from the patients were collected between 17-Dec-2014 and 23-Mar-2022. Informed consent was obtained from all patients. Ideally, informed consent had to be signed before baseline visit but it needed to be signed before any patient data were collected and entered into the case report form (CRF).

Patients and Study Size

Patients were included if they were aged ≥ 18 years old with confirmed diagnosis of IPSS low- or int-1-risk MDS with isolated del(5q) (with morphological and cytogenetic information), and who were transfusion-dependent or had an history of transfusion dependence. Patients who were participating in an interventional therapeutic clinical trial for MDS (except for erythropoiesis-stimulating agents and granulocyte colony-stimulating growth factors), who were receiving any investigational agent, or who had previously been treated with lenalidomide and were no longer

on active treatment with lenalidomide at the signing of the informed consent form (ICF) were not eligible to be enrolled in this study.

Three analysis populations were defined in this study:

- Primary population: The Primary population included all patients who had received at least 1 complete cycle of lenalidomide (for the Lenalidomide cohort only) as defined in the Revlimid (lenalidomide) Summary of Product Characteristics (SmPC) after ICF date (21-day cycles).
- Safety population: The Safety population included all patients who had received at least 1 dose of any drug or who had received any treatment modality after the patient signed the ICF.
- Sensitivity population: The Sensitivity population was defined as a subset of the Safety population. The Sensitivity population included all the patients of the Safety population who were transfusion-dependent IPSS low- or int-1-risk MDS and isolated del(5q).

The following 2 cohorts were defined for the Safety and the Sensitivity populations.

- Lenalidomide cohort: The Lenalidomide cohort included all patients who received at least 1 dose of lenalidomide.
- Background cohort: The Background cohort included all patients who received treatments or treatments modalities (i.e., any other treatment, excluding any dose of lenalidomide).

Patients in the Background cohort who switched to lenalidomide during follow-up contributed events and observation time to the Background cohort up to the first day of lenalidomide exposure; subsequent follow-up was attributed to the Lenalidomide cohort. Patient follow-up continued for a maximum of up to 3 years (or death, withdrawal of consent) from the date of informed consent signature regardless of whether the patient had switched therapies during the interval.

The summary of analysis populations is provided in the table below.

	Cohort	
Population	**Lenalidomide**	**Background**
Primary population (at least 1 complete cycle of lenalidomide)	☑	X
Safety population (at least 1 dose of any drug or treatment)	☑	☑
Sensitivity population (Safety population with transfusion-dependent IPSS low- or inter-1-risk MDS and isolated del[5q])	☑	☑

The study aimed to include at least 217 patients in the analysis dataset to obtain a 2-year cumulative estimate of AML progression with a precision of ± 5%. The target enrollment of 241 patients ensured that at least 217 patients were available for analysis based on a 10% loss to follow-up.

Variables and Data Sources

Demographics variables were as follows: age, sex, and country.

Clinical variables were as follows: date of MDS diagnosis, date of ICF signature, cytogenetic abnormalities, vital signs, bone marrow aspirate, bone marrow biopsy, peripheral blood morphology, prior MDS-associated therapy, TP53 status, RBC transfusion and platelet transfusion history, haematology, other laboratory tests, risk classification, pregnancy status, relevant medical history, and comorbidities.

Therapy and other treatment variables were as follows: current MDS treatments, prior therapy for MDS, and concomitant medications.

Outcome variables for safety were as follows: progression to AML, death, AEs, SPMs, haematology, and other laboratory tests.

Outcome variables for effectiveness were as follows: bone marrow aspirate, bone marrow biopsy, cytogenetic abnormalities, RBC and platelet transfusion, risk classification, and MDS response assessment.

Data from individual patient's charts were collected through a password-protected web-based electronic data capture system. The treating physician or an authorised delegate entered the data into the web-based electronic CRF based on the individual patient's charts. To protect privacy, data were anonymised and processed in accordance with local regulations regarding privacy protection. The sponsor managed the web-based system.

Results

The Primary population included 277 patients who received at least one complete cycle of lenalidomide. The primary objective of this study was to ascertain the progression to AML and OS among the Primary population with RBC transfusion-dependent, IPSS low- or int-1-risk MDS with del(5q) as an isolated cytogenetic abnormality who had been treated with lenalidomide. In the Primary population of this study, 2-year cumulative incidence of AML progression was 12.7% (95% confidence interval [CI]: 8.9% to 17.1%), and OS probabilities were 78.3% (standard error [SE]: 2.55) at 24 months and 63.9% (SE: 3.15) at 36 months.

The Safety population included 334 patients: 296 patients in the Lenalidomide cohort and 38 patients in the Background cohort. In the Lenalidomide cohort, most of the patients were female (77.7%) and the percentage of patients ≥ 75 years of age was 56.8%. In addition, 54.7% of patients were transfusion-dependent at baseline, and the remaining 45.3% had a history of transfusion dependence. The median duration of treatment in the Lenalidomide cohort was 16.89 months. In the Background cohort, most of the patients were female (89.5%) and the percentage of patients ≥ 75 years of age was 84.2%. In addition, 71.1% of patients were transfusion-dependent at baseline, and the remaining 28.9% had a history of transfusion dependence. The most frequently medication used for MDS treatment in the Background cohort was epoetin (alpha or beta) (39.5%), and 42.1% of the patients were treated only with transfusions and the median duration of treatment was 12.19 months.

In the Safety population, the 2-year cumulative incidence of AML progression in the Background cohort was 2.6% (95% CI: 0.2% to 12.0%). The OS probability at 24 months was 66.0% (SE: 8.10) in the Background cohort.

The most frequently reported Grade 3/4 treatment-emergent AEs (TEAEs) in the Lenalidomide cohort of the Safety population (≥ 2%) pertained to the system organ class of blood and lymphatic system disorders (45.6%), including neutropenia (26.4%), anaemia (19.3%), thrombocytopenia (12.8%), leukopenia (3.4%), and pancytopenia (3.0%), of which neutropenia and thrombocytopenia were the most frequently reported treatment-emergent adverse events of special interest. In the Lenalidomide cohort of Safety population, the TEAEs leading to death (≥2%) were acute myeloid leukaemia (4.7%) and transformation to acute myeloid leukaemia (2.0%).

The incidence rate of SPMs was 1.80 per 100 person-years (95% CI: 1.02 to 3.17) in the Lenalidomide cohort of the Safety population; the incidence rate of invasive SPMs was 1.34 per 100 person-years (95% CI: 0.70 to 2.58) and the incidence rate of non-invasive SPMs (non-melanoma skin cancer) was 0.44 per 100 person-years (95% CI: 0.14 to 1.38).

Discussion

This non-interventional PASS was conducted in 334 patients with transfusion-dependent, IPSS low- or int-1-risk MDS with del(5q) treated in the routine-care setting using lenalidomide or non-lenalidomide treatment modality in 11 countries in Europe. Data from patients were collected between 17-Dec-2014 and 23-Mar-2022. This study enabled the MAH to ascertain that the 2-year cumulative incidence of AML progression in MDS patients treated with lenalidomide in the routine-care setting was similar to what had been previously reported in the pivotal trials (MDS-003 and MDS-004). The current analysis of the results provides a robust picture of AML progression and survival (including risk factors) in patients who were treated with lenalidomide and non-lenalidomide treatment modalities as well as safety and effectiveness profile of lenalidomide.

The results of the PASS, as outlined above, indicate that the incidence of AML progression reported in Primary population of patients treated with lenalidomide in the routine-care setting is aligned with the incidences previously reported in interventional clinical studies involving patients with IPSS-low and int-1-risk MDS and del(5q) who were exposed to lenalidomide at the time of protocol development (17%).

Haematologic AEs were the most frequently reported Grade 3/4 AEs in this study, as in the pivotal study, Study MDS-004, which reported myelosuppression such as neutropenia thrombocytopenia, and anaemia in the combined lenalidomide cohort. In addition, neutropenia and thrombocytopenia are known as most commonly observed adverse reactions with lenalidomide when used for treatment of MDS as outlined in the most current Revlimid (lenalidomide) SmPC and the EU RMP.

The safety profile reported in this study has not raised any new safety signal or altered the overall benefit-risk profile of lenalidomide in its MDS indication, comparing with the safety profile reported in clinical trials, as outlined in the Revlimid (lenalidomide) SmPC and the EU RMP.

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